UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,237	10/10/2003	James S. Huston	CIBT-P02-130	3016

28120 7590 03/01/2007

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/684,237	HUSTON ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments in the Reply of 12/19/06 have obviated the election of species requirement of 8/1/06.

2. Claims 5 and 6 were amended to insert sequence identifiers. New Claim 50 is added.

3. Claims 1-32 and 50 are pending and under examination.

Information Disclosure Statement

4. The IDS filed 10/10/03 has been partially considered with respect to all U. S. Patents, however, all other documents have not been considered because the cited references were not in 09/55,741 or 08/462,641. The IDS has been placed in the file and if Applicants would supply a copy of the references, they will be considered at that time.

Specification

5. The disclosure is objected to because of the following informalities:

a. The preliminary amendment of 10/10/03 instructs the Examiner to amend the cross referencing of the application at paragraph 2. However, the amendment does not indicate the abandoned applications and the reference to the 07/831,967 application appears in duplicate.

b. The specification is objected to because it does not provide sequence identifiers for the following sequences pursuant to 37 CFR 1.821 (c) and/or (d):

pp. 11 and 30, $(Gly)_4$-Cys;

pp. 11 and 30, $(His)_6$-$(Gly)_4$-Cys

pp. 12 and 32, $GlySer_3Gly_2Ser_3Lys$

p. 39, Ile-Glu-Gly-Arg

p. 39, AspAspAspAspLys

Applicants are required to identify the above-referenced sequences with sequence identifiers in addition to any other sequences that may not be properly identified in the specification and drawnings.

Claim Objections

6. Claims 1 and 13 are objected to for an apparent typographical error:

a) Claim 1 contains a double repeat "and and" in element a) of the claim.

b) Claim 13 recites "form" and seemingly should recite "from".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-32 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-32 and 50 are indefinite for reciting that the construct comprises "a C-terminal tail" in claims 1-3 and 50 because the exact meaning of the phrase is not

clear. What C-terminal is being referred to: does the phrase mean that the polypeptide chain has a tail on the C-terminus or is the tail C-terminal to each of the polypeptide domains for a polypeptide chain?

b. Claims 1-32 and 50 are indefinite for the recitation "a crosslinking means" in Claims 1-3, 9, 12 and 50 because it is not clear what structure or physical moiety is contemplated for providing the crosslinking aspect to the C-terminal tail.

c. Claims 2-32 are indefinite for the recitation "for binding preferentially to a preselected antigen" in Claims 2 and 3 because the exact meaning of the term "preferentially" is not clear. The meaning of the term is not defined in the claim or the specification, and one cannot ascertain whether the construct has apparent cross-reactivity with an antigen(s) other than the "preselected antigen" much less whether the construct has an apparent specificity for the preselected antigen.

d. Claim 13 is indefinite for reciting improper Markush group language "selected form group of". Appropriate correction is required.

e. Claim 19 is indefinite for the recitation "forms a substantially inflexible structure" because the term "substantially" is not defined by the claim or specification, and one cannot ascertain the degree or extent of inflexibility the structure must achieve in order to be substantial.

f. Claim 32 is indefinite for the recitation "has improved in vivo imaging characteristics" because it is not clear what baseline or standard the imaging characteristics are being compared with in order for them to be improved and what constitutes a change in the imaging characteristics to be an improvement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

8. Claims 1-32 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for scFv, dimeric scFv and bispecific scFv having the VH and VL domains from the corresponding parent antibody cloned into the respective constructs, does not reasonably provide enablement for constructs containing anything less than a VH and VL domain each comprising 3 CDRs interposed between 4 framework regions in the proper order of the parent antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

The nature of the invention is drawn to a formulation comprising a scFv or dimeric scFv or bispecific scFv where the relative skill of those in the art is deemed to be high.

The claims are not commensurate in scope with the enablement provided in the specification. The specification teaches and is enabling for scFv, dimeric scFv and bispecific scFv having the VH and VL domains from the corresponding parent antibody cloned into the respective constructs, where each VH and VL domain comprises CDR1-3 and FR1-4. But, the specification is not enabling for constructs containing anything less than an intact VH and VL domain where the criticality of the CDRs and FRs is fully appreciated for antigen binding.

In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al. Science 233: 747-753, 1986).

Furthermore, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin.

It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper

association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Coleman (Research in Immunol. 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (p. 35, top left col. and p. 33, right col.). It is unlikely that scFvs which contain less than the full complement of CDRs and FRs from the light and heavy chain variable regions in their proper order and in the context of framework sequence much less amino acid substituted frameworks, which maintain the correct spatial orientation for antigen recognition have the required preselected antigen binding function. It is unlikely that the polypeptide as defined by the claims which may contain incomplete set of CDRs or FRs, have the required binding function. The specification provides no direction or guidance regarding how to produce polypeptides as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional binding polypeptide can be obtained by using a binding domain having anything less than the full complement of 6 CDRs and the full complement of 4 FRs in proper order.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above regarding the lack of predictability as evidenced by Amit, Rudikoff, and Coleman one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a dimeric scFv and scFv molecules. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Priority

9. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 07/831,967 (filed 2/6/92 and now abandoned; hereinafter referred to as "'967", which is parent to continuation Application No. 356,786, and which issued as USPN 5,877,305), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The instant claims are drawn to scFv having a non-self associating C-terminal tail which permits crosslinking between the scFv polypeptides to create dimeric structures, where the C-terminal tail comprises Ser-Cys, or $(Gly)_4$-Cys or $(His)_6$-$(Gly)_4$-Cys.

The '967 application discloses the scFv construct having a linker situated between the VH and VL domains from a parent antibody, and fusion proteins where a second molecule of interest is fused to the scFv, but the '967 application does not even contemplate using/inserting C-terminal structures such as a leucine zipper or amino acid peptides that are cross-linkable to create dimeric forms of the scFv directed to the same antigenic determinant much less bispecific molecules. Thus, none of the pending claims for the instant application obtain benefit of the '967 filing date of 2/6/92, and for purposes of examination and prior art, the claims are given benefit of the 10/7/93 filing date for the 08/133,804 application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-11, 14-16, 18, 24-26, 30-32 and 50 are rejected under 35 U.S.C. 102(a) as being anticipated by Adams et al. (Can. Res. 53:4026-4034 (Sept. 1, 1993).

Claims 1-11, 14-16, 18, 24-26 and 30-32 are broadly drawn to scFv having a VH and VL domain linked by a polypeptide and further comprising on the C-terminal of the scFv a tail that provide for crosslinking and a linkage coupling for forming a dimer with the ability to bind a preselected antigen, where the C-terminal tail comprises amino acid

sequence Ser-Cys, $(Gly)_4$-Cys or $(His)_6$-$(Gly)_4$-Cys or chelates ions such as a metal ion, where the linkage is a disulfide bond, where the linkage is a derivatizable amino acid such as lysine or cysteine, or a chemical bridge or disulfide bond or a bismaleimidohexane cross-linker or a peptidyl linker, where the dimeric construct targets an antigen with greater avidity than either polypeptide chain individually, where the antigen is preselected on the surface of a cell, where one of the binding sites binds a therapeutic agent for targeting a cell surface and the agent is cytotoxic, where the dimeric construct has improved in vivo imaging characteristics. Claim 50 is drawn to a formulation comprising the dimeric construct for binding an epitope on a therapeutic agent for cell targeting when administered in a mammal.

Adams disclose tumor-specific scFv directed against the c-erbB-2 antigen and compared them to control scFv species specific for the cytotoxic drug, digoxin. ScFv and divalent disulfide-bonded (scFv')2 moelcules having C-terminal cysteine residues to facilitate site-specific dimerization were examined for binding in vitro and in vivo tumor imaging by targeting mice bearing tumor xenografts expressing c-erbB-2 antigen. Adams teaches that to introduce more steric flexibility into the divalent (scFv')2, longer spacers were used to join the monovalent scFv' units: Gly4Cys2Gly4 (Gly4Cys), MAC-Gly-Ser3Gly2Ser3Lys-MCA; and the homobifunctional cross-linker bismalimidohexane. Adams discloses whole body imaging with radiolabeled (scFv')2. Adams discloses improved avidity

For all of these reasons, the claims were anticipated by Adams.

11. Claims 1-3, 7, 8, 15, 19, 25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Pack et al. (Biochemistry 31:1579-1584 (Feb. 18, 1992) as evidenced by Liu et al. (Curr. Prot. And Pep. Sci. 2:107-121, 2001).

The interpretation of Claims 1-3, 7, 8, 15, 19, 20, 25 and 28 is discussed supra.

Pack discloses that dimeric as well as tetrameric mono- and bi-specific Fv fragments with potential diagnostic and therapeutic application can be produced, assembled, and secreted by E. coli using amphipathic helical structures inserted into the scFv polypeptide C-terminus. Pack discloses the components and structure of a dimeric monospecific Fv miniantibody comprising the Fv fragment of the McPC603 Mab consisting of VH, the artificial linker (Gly, Gly, Gly, Ser), and where the VL was followed by an artificial hinge sequence (Pro, Lys, Pro, Ser, Thr, Pro, Pro Gly, Ser, Ser), the GCN4 leucine zipper, and an artificial tail (Gly, Gly, Cys, Gly, Gly). Pack discloses that the dimeric scFv show a gain in avidity. The model for the dimeric Fv fragment of McPO603 and sequences of linker, hinge, GCN4 leucine zipper, and cysteine tail using the one-letter amino acid code of Pack is depicted in Figure 3 as evidenced by Liu.

For all of these reasons, the claims were anticipated by Pack as evidenced by Liu.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-32 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 and 26-30 of U.S. Patent No. 5,534,254 (the "254'" patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because Claims 1-32 and 50 being drawn to a formulation comprising dimeric scFv could be readily interpreted by one skilled in the art as being the same as the composition comprising a scFv in Claims 1-21 and 26-30 of '254.

The interpretation of Claims 1-11, 14-16, 18, 24-26, 30-32 is discussed supra. Claims 12, 13, 17, 19-23 and 27-29 are drawn to formulations comprising the construct comprising a crosslinking means comprising a a posttranslationally modified amino acid, where the amino acid is the Asn residue located in the amino acid sequence selected form group of Asn-Xaa-Ser and Asn-Xaa-Thr, where the linkage comprises a bismaleimidocaproyl amino acid linker, where the linkage forms a substantially inflexible structure under physiological conditions, where the linkage has a length and

composition optimized for binding of two preselected antigens expressed on a tissue surface in a mammal, linkage comprises a detectable moiety such as Technetium^{99m}, where the detectable moiety comprises means for inducing proton relaxation in vivo, where the antigen is an intracellular component exposed upon cell lysis, where the dimeric construct binds two different epitopes, where the binding sites further comprises a catalytic site.

The claimed formulation would have been prima facie obvious at the time the invention was made over Claims 1-21 and 26-30 of the 254' patent because one skilled in the art could reasonably interpret a formulation as being the same as a composition.

Claims 1-21 and 26-30 of '254 are drawn to compositions for targeting antigens expressed in a mammal, comprising a dimeric construct comprising a two polypeptides and defining a scFv with two polypeptide domains connected by a linker were each domain comprises CDRs interposed between framework regions, and the domains forming a binding site, where each polypeptide chain comprises a C-terminal tail essentially free of helical character and comprising derivatizable amino acid side chain, where the scFv coupler linking each scFv occurs through the derivatizable side chain, where the C-terminal tail comprises Ser-Cys or $(Gly)_4$-Cys or $(His)_6$-$(Gly)_4$-Cys or chelate ions such as metal, where the amino acid of the derivatizable group is lysine, arginine and histidine or cysteine, where the coupler is a chemical bridge or dislulfide bond orbismaleimidohexane cross-linker or bismaleimeidocaproyl amino acid linker, where the scFv comprises a detectable moiety such as Technetium^{99m} and the detectable moiety comprises means for inducing proton relaxation in vivo, where the

construct targets an epitope on the antigen with greater avidity than either scFv individually, where the antigen is expressed on a cell surface, where the antigen is intracellular, where the construct binds two different epitopes, where the polypeptide chains comprise a detectable moiety such as a radioactive atom.

Because Applicants contemplated and claimed the C-tail elements, one skilled in the art could have readily have introduced the elements into the invention of generic claims 1, 2 and 3, thus the combination of instant Claims 1, 4-6 and 9, Claims 2, 4-6 and 9, and Claims 3-6 and 9 as drawn to scFv constructs comprising a C-terminal tail essentially free of helical character (Claims 4-6) and/or further comprising derivatizable amino acid side chain (Claim 9), are rendered obvious over the claims of the '254 patent.

12. Claim 50 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,534,254 (the "254'" patent) in view of Adams as discussed supra. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 50 being drawn to a formulation comprising dimeric scFv which recognized a therapeutic agent for targeting could be readily interpreted by one skilled in the art as being the same as the composition comprising a scFv in Claims 1 or 2 of '254 patent and in view of Adams who discloses that the scFv construct recognize a therapeutic moiety or agent for being targeted, where the scFV of Adams recognized digoxin.

Thus, the claim was prima facie obvious at the time of the invention over the '254 patent and Adams.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER